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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/398,405	09/16/1999	JOHN C. SALERNO	JCS96-01Z	1062

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EXAMINER
CANELLA, KAREN A

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 12/12/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/398,405	Salerno
Examiner	**Art Unit**
Karen Canella	1642

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3 months* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-59* is/are pending in the application.

4a) Of the above, claim(s) *1-30, 34-47, and 51-59* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *31-33 and 48-50* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *5*
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

1. Please note that the examiner assigned to this application has changed.

2. Acknowledgment is made of applicants election with traverse of Group 35, drawn to a method of activating endothelial nitric oxide synthase wherein the activator is a peptide and a method of treating a disease comprising administering a peptide. The traversal is on the grounds that the restriction is improper as it separates inventions comprising co-extensive subject matter. after consideration of the applicants arguments, Groups 34 and 36 are joined to the elected group, and the species election requirement of Paper No. 9 is withdrawn. The elected group now stands as being drawn to methods of activating endothelial and neuronal nitric oxide synthase comprising contacting the nitric oxide synthase with the peptide comprising SEQ ID NO:4-9 or an agent which antagonizes auto-inhibition by a peptide region of nitric oxide synthase, wherein this peptide region is 590-650 of eNOS and 820-880 of nNOS, and methods of treating disease modulated by the production of eNOS or nNOS comprising administering a peptide comprising SEQ ID NO:4-9 or an agent which antagonizes auto-inhibition by a peptide region of nitric oxide synthase, wherein this peptide region is 590-650 of eNOS and 820-880 of nNOS.

3. Claims 1-59 are pending. Claims 1-30, 34-47 and 51-59, drawn to non-elected inventions are withdrawn from consideration. Claims 31-33 and 48-50 are examined on the merits.

Specification

4. The specification is objected to as not complying with 1.821(d) of the Sequence Rules and Regulations. On pages 20, 29, 32, 33, 34 and 35 the specification refers to peptide sequences without an appropriate sequence identifier. When the specification of a patent application discusses a sequence listing that is set forth in the "Sequence Listing" in accordance with paragraph (c) of the Sequence Rules and Regulations, reference must be made to the sequence

by use of the assigned identifier, in the text of the description or claims of the patent application. Further, RRKRK is labeled as SEQ ID NO:7 on page 4 and as SEQ ID NO:10 on page 16. Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 31-33 and 48-50 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 31-33 and 48-50 are rendered unclear as they are drawn to the non-elected inventions of claims 16, 19 and 20.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

8. Claim 31 is rejected under 35 U.S.C. 102(b) as being anticipated by Ohashi et al (Biochemical and Biophysical Research Communications, 1993, Vol. 195, pp. 1314-1320). Claim 31 is drawn to a method for activating endothelial nitric oxide synthase comprising contacting said synthase with an agent that antagonizes the autoinhibition of the eNOS, said autoinhibition arising from the region of amino acids 590-650 of eNOS. Ohashi et al disclose a

method of activating endothelial nitric oxide synthase by contacting said eNOS with the phospholipids of phosphatidylcholine, lysophosphtidylcholine and phosphatidylethanolamine. Ohashi et al disclose that these phospholipids enhanced the activity of eNOS in the presence of calcium, calmodulin, NADPH, FAD and tetrahydrobiopterin. Given that activating ability of the lysophopholipids were additive to the activating ability of calmodulin, NADPH, FAD and tetrahydrobiopterin, it is reasonable to assume that said phospholipids did not bind to eNOS in the sites occupied by calmodulin, NADPH, FAD and tetrahydrobiopterin, but activated eNOS by antagonizing the autoinhibition of amino acids 590-650 of eNOS. The Office does not have the facilities and resources to provide the factual evidence needed in order to establish that the method of the prior art is not directed to the same functional characteristics of the claimed antagonists of autoinhibition. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed method is different from those taught by the prior art. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

9. Claim 33 is rejected under 35 U.S.C. 102(b) as being anticipated by either Hu et al (NeuroReport, 1993, Vol. 4, pp. 760-762) or Hashida-Okumura et al (J of Clinical Biochemistry and Nutrition, 1994, Vol. 17, pp. 141-151). Claim 33 is drawn to a method for activating neuronal nitric oxide synthase comprising contacting said synthase with an agent that antagonizes the autoinhibition of the nNOS, said autoinhibition arising from the region of amino acids 820-880 of nNOS. Hu et al teach a method of activating neuronal NOS by contacting nNOS the B-amyloid peptide, amino acids 25-35. Hashida-Okumura et al teach a method of activating brain NOS comprising contacting said NOS with a partially purified factor isolated from human urine. These reference do not specifically teach that the activating agents used in the disclosed methods activate nNOS by antagonizing autoinhibition from amino acids 820-890 of nNOS. However, the claimed methods appears to be the same as the prior art methods. The Office does not have

the facilities and resources to provide the factual evidence needed in order to establish that the method of the prior art is not directed to the same functional characteristics of the claimed antagonists of autoinhibition. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed method is different from those taught by the prior art. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

10. Claims 32 and 48-50 are rejected under 35 U.S.C. 102(e) as being anticipated by Schrader et al (US 6,149,936). Claim 32 is drawn to a method of activating endothelial nitric oxide synthase comprising contacting said synthase with an agent which comprises SEQ ID NO: 4-9. Claims 48 and 49 are drawn to a method of treating a disease modulated by the production of eNOS comprising administering an agent which antagonizes the autoinhibition of the eNOS, said autoinhibition arising from the region of amino acids 590-650 of eNOS or administering a peptide comprising the amino acid sequences of SEQ ID NO:4-9. Claim 50 is drawn to a method of treating a disease modulated by the production of nNOS comprising administering an agent which antagonizes the autoinhibition of the nNOS, said autoinhibition arising from the region of amino acids 820-880 of nNOS. The specification discloses that SEQ ID NO:4 and 5 are the negatively charged loops of iNOS, SEQ ID NO:6 and 7 are the negatively charged loops of eNOS and SEQ ID NO:8 and 9 are the negatively charged loops of nNOS. Schrader et al disclose a method of treating vascular disorders comprising the administration of DNA encoding iNOS, eNOS or brain NOS, for the in vivo expression of the peptides comprising the amino acid sequences of SEQ ID NO:4-9. Although the reference does not teach that the recombinant expression of iNOS, eNOS or brain NOS antagonizes the autoinhibition of eNOS or nNOS, the reference does teach the administration of peptides **comprising** SEQ ID NO:4-9 for treating a disease modulated by the production of NOS. Therefore the antagonism of autoinhibition of eNOS and nNOS is inherent in the method of Schrader et al.

Conclusion

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella, Ph.D.
Patent Examiner, Group 1642
December 10, 2001